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Review

Fibroblast Growth Factor Receptor 2 Signaling in Breast Cancer

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Abstract

Fibroblast growth factor receptor 2 (FGFR2) is a membrane-spanning tyrosine kinase that mediates signaling for FGFs. Recent studies detected various point mutations of FGFR2 in multiple types of cancers, including breast cancer, lung cancer, gastric cancer, uterine cancer and ovarian cancer, yet the casual relationship between these mutations and tumorigenesis is unclear. Here we will discuss possible interactions between FGFR2 signaling and several major pathways through which the aberrantly activated FGFR2 signaling may result in breast cancer development. We will also discuss some recent developments in the discovery and application of therapies and strategies for breast cancers by inhibiting FGFR2 activities.

Key words: Breast cancer, FGFR2, mutation, polymorphism, inhibitor.

Introduction

Fibroblast growth factor receptor 2 (FGFR2) belongs to a family of four typical membrane-bound receptor tyrosine kinases (RTKs) [1-4]. Although an additional FGF receptor, FGFR5, has been identified, it does not contain the intracellular tyrosine kinase domain [5]. FGFRs mediate signaling from fibroblast growth factors (FGFs), which constitute of a gene family of at least 22 members and have numerous important functions, including developmental induction, pattern formation, cell growth and differentiation, as well as survival and death [1-4]. It has been shown that mutations of FGFRs were able to facilitate tumor growth by driving cell proliferation and survival [6], but also could suppress tumor growth [7]. Consistently, studies of mouse models have revealed that FGFR2 not only serves as an oncogenic gene [8, 9], but also acts as a tumor suppressor in a certain intracellular environment [10-12].

In this review, we discuss insights into the mechanism of FGFR2 regulation that has emerged from structural and functional studies. We will review the integrated networks that result from the interplay among the complex signaling pathways activated by FGFR2 during breast cancer formation. Finally, we will explore the applications of therapies and strategies for breast cancers driven by FGFRs activities in clinical conditions.

Structure of *FGFR2* and its signaling pathways

The *FGFR2* gene is located at chromosome 10q26 and contains 20 exons in humans and 19 exons in the mouse. *FGFR2* encodes two major isoforms through alternative splicing, FGFR2b and FGFR2c, which have distinct function domains that specifically recognize a variety of fibroblast growth factors (FGFs) [1, 13-16]. As a membrane bound receptor, FGFR2 contains an extracellular region, which is made up of signal peptides (SP), three immunoglobulin domains (D1, D2, and D3) and an acid box (AB) [17]. This is followed by a cross-membrane domain, a split tyrosine kinase (TK) domain (including TK1 and TK2) and a short carboxyl-terminal tail (Figure 1).

The FGFR2 signaling pathways divide into two streams. One is dependent on FGFR substrate 2α (FRS2α) [18], while the other is not. It is involved in

major four pathways, including RAS-MAPK (mitogen-activated protein kinase), PLCγ (Phospholipase C-γ), PI3K (phosphoinositide 3-kinase), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) (Figure 2). FGFR2 acts through multiple downstream signaling pathways that play vital roles in cell proliferation [12, 19, 20], survival [21], differentiation [22] and drug resistance [23]. FGFR substrate 2 (FRS2) is a key adaptor protein that binds to the juxtamembrane region of FGFR2 through its phosphotyrosine-binding (PTb) domains. The activated FGFR2 phosphorylates FRS2 on several sites, allowing the recruitment of the adaptor proteins 'Son of Sevenless' (SOS) and growth factor receptor bound 2 (GRb2) to activate RAS and the downstream MAPK pathways. A separate complex involving GRb2 associated binding protein 1 (GAb1) recruits a complex, which includes PI3K, and this activates a PI3K-AKT signaling pathway. Another FGFR2 binding partner is phospholipase Cγ (PLCγ), which binds at the carboxyl-terminal tail on auto-phosphorylation of FGFR2. After PLCγ is activated, it hydrolyses phosphatidylinositol 4,5 biphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3) and diacylglycerol (DAG), activating protein kinase C (PKC), which enhance the stimulation of the MAPK pathway by phosphorylating RAF. Several other pathways are also activated by FGFR2, such as the JAK-STAT pathway [24] (Figure 2).

Amplification of FGFR2 in breast cancer

Breast cancer occurs in women worldwide and is the causes of the highest cancer lethality in females of developing countries [25]. Currently about 1.7 million cases of breast cancers and about half million deaths are reported annually in 2012 [26]. With increasing incidence and mortality, breast cancer will certainly be a big public problem not only in developing countries, but also in developed countries.

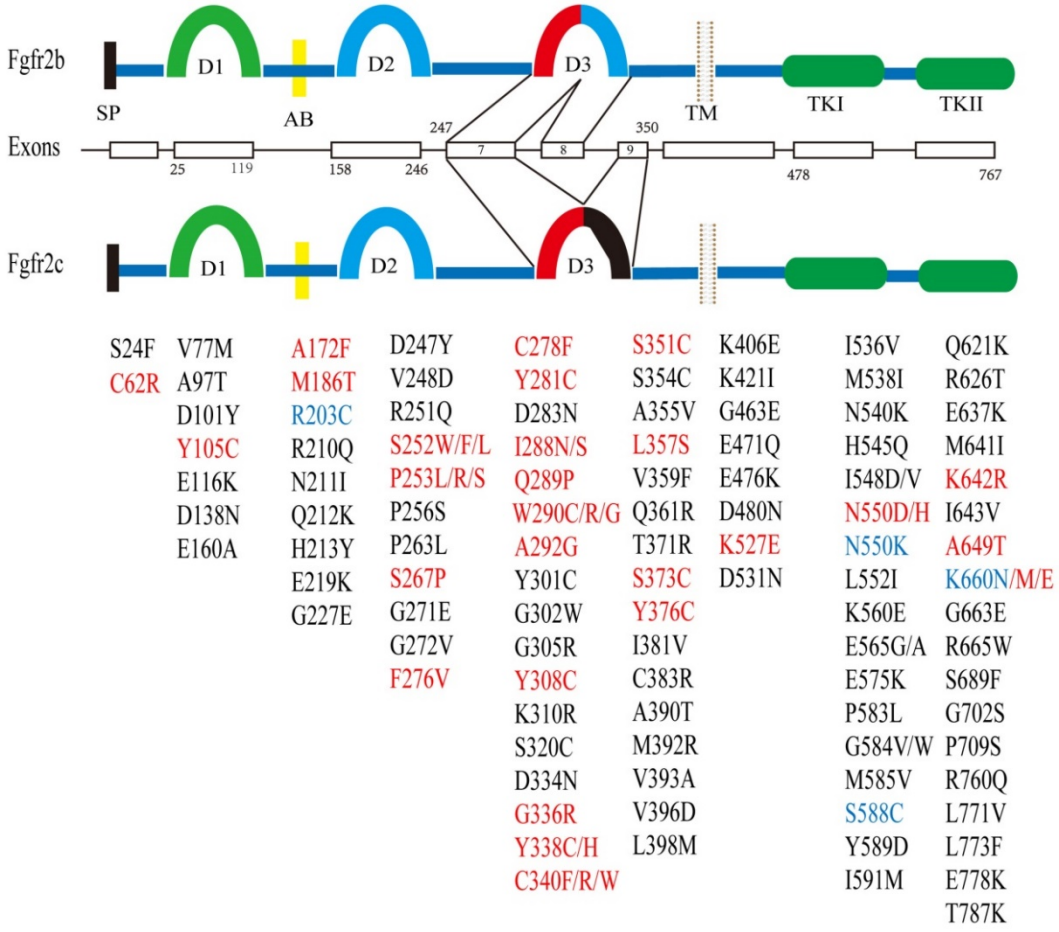

Figure 1. Structure of the FGFR2 gene and its somatic mutations with their relative locations. There are two major isoforms of FGFR2, i.e. FGFR2b (upper), and FGFR2c (lower) that are caused by alternative splicing of exons 8 and 9. Both isoforms contain multiple functional domains as indicated. SP: signal peptide; D1-3: immunoglobulin I-III; AB: acid box; TM: transmembrane; TK: tyrosine kinase. Somatic mutations in FGFR2 identified in development syndrome and cancers are presented in red font, and in breast cancer is highlighted in blue font. Mutations present only in cancer are shown in black font. The residue numbers are according to Table 3.

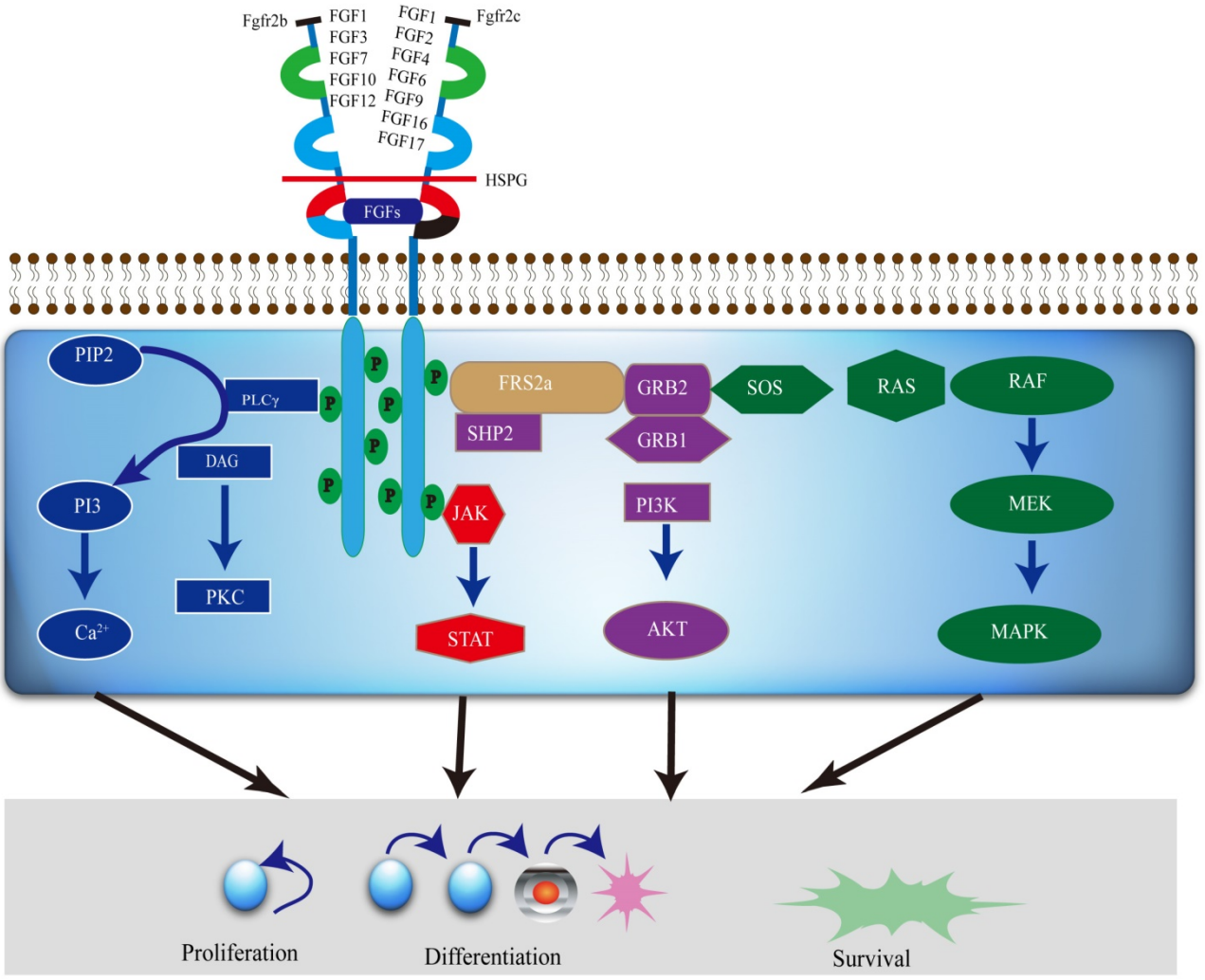

Figure 2. A diagram of the FGFR2 mediated signaling pathways. Various FGFs bind to FGFR2b or FGFR2c, respectively, with HSPG as a cofactor and induce the formation of ternary FGFs-FGFR2-HS complex, which activates the FGFR2 intracellular tyrosine kinase domain by phosphorylation of specific tyrosine residues. The activated TK of FGFR2, in turn, triggers activation of multiple downstream signaling pathways, which not only regulate differentiation and gene expression in the nucleus, but also drive cell proliferation and survival as well.

Multiple genetic aberrations in FGFR2 triggering the activation of up and/or downstream FGFR2 signaling pathways have been identified in breast cancer. For instance, 6 out of 165 (3.6%) of triple-negative breast cancers (TNBC) has been found to carry an amplification of FGFR2 (10q26) [27]. Researchers also screened 51 breast cancer cell lines and found two of them, MFM223 and SUM52PE, carry FGFR2 genes amplification and protein overexpression. Both cell lines were confirmed to be (TNBC) cell lines, and the amplification of FGFR2 results in the activation of PI3K-AKT signaling, leading to the inhibition of apoptosis [27]. FGFR2 gene amplification is not only found in breast cancer cell lines, but also in normal breast and tumor tissues [28-30]. In addition, Sun *et al.* (2011) reported that 64.8% (81/125) and 56.8% (71/125) of breast cancers expressed FGFR2 in cytoplasm and the nucleus, respectively. They showed that FGFR2 expression in cytoplasmic was significantly associated with tumor size and the tumor, node and metastasis (TNM) stage, and higher levels of FGFR2 in the cytoplasm and nucleus were associated with much lower overall survival and disease-free survival rates than lower levels of FGFR2 [31]. However, Lee *et al.* (2014) reported that FGFR2 amplification did not affect patient survival [32].

In vitro studies showed that FGFR2 activates ERK directly and binds to phosphorylation POU1F1 at thr75, which inhibits transcription of the double-strand break repair protein Mre11A (Mre11) via interaction with the Mre11 promoter, and promotes breast cancer formation [33]. Wei *et al.* (2015) expressed FGFR2 in MCF-7 cells and found that FGFR2 activates HER2 through FGF7/FGFR2-mediated ADAM10 upregulation, which results in the enhanced AKT, STAT3, ERK1/2 signaling leading to the activation of HER2 [34, 35].

Ezzat *et al.* (2012) found that FGFR2 regulates epithelial cell-stromal cell communications through tissue-specific FGF signals in cancer progression. In addition, their data also indicated that FGFR2 isoforms negatively regulate NF-kB nuclear translocation and activity, and reduce the growth of MDA-MB-231 tumor cells [36]. FGFR2 was also found to facilitate the development of breast cancer by promoting cell self-renewal through interacting with NF-kB signals [37].

Table 1. Single Nucleotide Polymorphisms (SNPs) in intron 2 of FGFR2

SNPs ID	Population	Number Case /Control	OR(95%CI)	Ref.
rs35054928	Mix	93010/107391	1.05 (0.93-1.18)	[89-91]
rs45631563			0.80 (0.76-0.85)	
rs11200014			1.10 (0.84-1.21)	
rs2981579			1.20 (1.11-1.29)	
rs2303568	China	2073/2084	0.94 (0.78-1.13)	[92]
rs755793			1.00 (0.80-1.12)	
rs3135730			0.93 (0.78-1.12)	
rs1078806			0.94 (0.75-1.22)	
rs2981582	Mix	93010/107391	1.22 (1.18-1.27)	[51, 93-97]
rs7895676			1.22 (0.97-1.48)	
rs1219648			1.23 (1.19-1.26)	
rs2420946			1.23 (1.18-1.29)	
rs2981578			0.81 (0.79-0.83)	
rs1078806			1.20 (1.04-1.38)	
rs3750817			0.85 (0.79-0.91)	
rs3135718			1.27(1.14-1.41)	
rs2981575	European	1187/1193	0.88 (0.78-0.99)	[98]
rs1078806	Sardinian	1698/2178	0.77 (0.69-0.86)	[99]
rs2860197			0.76 (0.68-0.86)	
rs2912774			0.77 (0.68-0.86)	
rs2912780			1.30 (1.16-1.46)	
rs2936870			0.77 (0.68-0.86)	
rs3135774	American	3663/4687	1.47 (1.18–1.83)	[61]
rs10736303	North	1247/1105	1.25 (1.18-1.32)	[88, 100]
rs2162540	Carolina		1.31 (1.15-1.48)	
rs1896395	Europe	1972/1776	0.87 (0.69–1.10)	[101]
rs17102287	China	388/428	1.08 (0.88 -1.34)	[102]
rs17542768			1.28 (0.88-1.87)	
rs10510097			0.86 (0.68-1.07)	

Note: Mix—China, Europe, Japan, American, Taiwanese, *et al.*

A further relationship between the FGFR2 signaling pathway and breast cancer has been illustrated by using GWAS (Genome-wide association study) [38, 39]. Analyzing 4,398 (women with breast cancer) familial breast cancer causes and 4,316 controls, five single nucleotide polymorphisms (SNPs) (rs7895676, rs2912781, rs10736303, rs2912778 and rs2981582) and in the non-coding region of FGFR2 were found to have a significant association with breast cancer [38]. Meanwhile, Hunter *et al.* (2007) also identified four other SNPs, rs11200014, rs2420946, rs1219648 and rs2981579, in intron 2 of FGFR2 that are associated with the risk of breast cancer [39]. So far, a much greater breast cancer risk associated SNPs have been discovered in intron 2 of FGFR2 (Table 1). FGFR2 polymorphisms are a risk factor associated with increased breast cancer (BC) susceptibility, these associations vary in different ethnic populations, such as China, Japan, Indian, Pakistani African American, Europe and so on, yet how they enhance breast cancer risk remains elusive.

Breast cancer associated gene 1 and 2 (BRCA1 and BRCA2) are related to a family history of breast cancer. Women having germline mutations in BRCA1 have a 50–80% risk of developing breast cancer by 70 years of age [40-45]. In BRCA1-associated tumors showed increased expression of the FGFR2 gene [46], particularly in ER-α positive breast cancer [47]. SNPs in the FGFR2 gene were associated with a significantly increased risk of luminal A, luminal B (ER/PR+, HER2+), or HER2+/ER- disease, but none were associated with basal-like (ER-, PR-, HER-) disease [48]. In BRCA1 carriers, rs2981582 of FGFR2 showed significant differences with a strong association for ER-positive or PR-positive disease but not ER-negative or PR-negative disease. There were no differential associations between ER states and PR status in BRCA2 mutation carriers [49, 50]. Interestingly, the GA and AA genotypes of FGFR2 rs2981582 are associated with a reduced the rate of breast cancer in Heilongjiang Province in Northeast China [51], whereas the AA genotypes of FGFR2 rs2981582 had an increased breast cancer risk in the Swedish population [52]. These contradictory observations suggest that gene-gene or gene-environmental interaction regulates the corporation between SNPs and the risk of breast cancer in difference regions or ethnics. Furthermore, SNPs (rs1078806, rs2420946, rs2981579, rs2981582) in intron 2 of FGFR2 is more highly linked to ER-positive and PR-Positive than ER-negative cancers in European and Asian [53, 54]. However, rs1219648 exhibited no differences associated between ER-positive cancer, ER-negative cancer and TNBC [55]. Amusingly, Andersen, *et al.* (2014) using 869 postmenopausal breast cancer cases and 808 postmenopausal community controls to evaluate rs1219648 for the association risk of breast cancer and found FGFR2 rs1219648 is more strongly associated with risk in estrogen-only hormone users [56]. Meanwhile, in a Chilean population, rs2981582, rs2420946 and rs1219648 are more significantly linked to familial breast cancer and early-onset non-familial breast cancer [57, 58]. One study suggested that rs2981582 and rs1219648 not only interacts with transcription factors Oct-1/Runx2, but C/EBPβ binding sites as well. Further study suggests that FGFR2 acts through ER and OCT1 activates C/EBPβ transcription [59], which may be a reason why the risk

of rs2981582 is strongly associated with ER-positive but not ER-negative breast cancer [60]. Indeed, further analysis revealed that rs2981582 is associated with all breast cancer tumor types except ER-/PR- tumors [61, 62]. It was also shown that Histone3/4 acetylation is involved in downstream splicing sites of FGFR2 in breast cancer, and rs2981578 harbors a potential Oct/Runx2 binding site displaying H4 deacetylation [63]. These transcription factors are occupied *in vivo* and lead to increased FGFR2 expression. Moreover, Murillo *et al.* (2013) suggested that rs2981582 is strongly associated with breast cancer not only in alcohol consumption in Mexican women [64], but also in physical activity (swimming, running, and playing basketball, etc.) in Guangzhou as well [65]. Studying 457 male breast cancer cases and 1073 healthy male and female controls, Nick *et al.* (2011) found rs2981579 in FGFR2 increases susceptibility to male breast cancer in the first instance [66]. Additionally, Nadezhda *et al.* (2011) found SNPs in FGFR2 and TP53 are cooperatively associated with breast cancer in Caucasian patients, particularly in the postmenopausal period [67]. Thus, SNPs of FGFR2 drive themselves to associate with breast cancer and may contribute to cancer initiation and development. Although our understanding of these SNPs in intron 2 of FGFR2 in breast cancer remains limited, these SNPs may serve as important clinically markers for breast cancer prediction or diagnosis.

Point mutations in FGFR2

Many point mutations in FGFR2 have been reported to cause multiple types of craniosynostoses (Table 2), including Apert syndrome (AS), Crouzon syndrome (CS), Beare-Stevenson syndrome (BS) and Pfeiffer syndrome (PS) etc. Meanwhile, much more mutations were found in various cancers, including those found in craniosynostoses (Figure 1). The cancer types include endometrial carcinomas (12%) [68], lung cancer (3%), skin cancer (rarely), gastric cancer (6%) [69], uterine cancer (rarely), ovarian cancer [70] and breast cancer (4%) [27, 71] (Table 3). Like the point mutations that cause skeletal abnormalities, these point mutations also occur throughout FGFR2, including the ligand-binding and transmembrane domains, and TK domain as well [72].

Nadine *et al.* (2013) mutated R203C and K660N in FGFR2 and expressed them in HEK293 cells, the result demonstrated both of mutations increased tyrosine kinase activity although K660N mutant was stronger than R203C mutation. Byron *et al.* (2013) used dovitinib (pan-FGFR inhibitor) to screen for drug-resistant mutations and study the underlying mechanism of drug-resistant [73]. After treating the BaF3 cell line over expressing FGFR2 with high concentration of dovitinib, they identified 14 dovitinib-resistant mutations, including the N550K, which is also observed in breast cancer. Their data demonstrated that the potential mechanism underlying drug resistance is increased receptor tyrosine kinase activity [73].

Table 2. Mutations in FGFR2 identified in diverse human syndrome

Human skeletal Disease	Mutation	Ref.
Apert syndrome (AS)	M186T, P252S/W/F/L, P253L/R, S267P	[103-105]
Beare-Stevenson syndrome (BS)	Y375C, S372C	[106]
Crouzon syndrome (CS)	A315T/S, A344G/P, C278F, F276V, G338R, K526E, N549D/K/H, Q289P, S267P, S347C, S354C, Y105C, Y281C, Y340C/H	[9, 104, 107-109]
Pfeiffer syndrome (PS)	A172F, A314D, C278F, C342F/R/S, K641R, N549D/K, S267P, T341P, W290C, Y340C/H	[9, 104, 110, 111]

Table 3. Mutations in FGFR2 identified in diverse human cancers

Human Cancer Disease	Mutations	Ref.
Adenoid cystic carcinoma	K642R, Y376C	[109, 112, 113]
Bladder cancer	M186T	[114]
Breast cancer	R203C, N550K, S588C, K660M	[68, 109, 112, 115, 116]
Cervical cancer	A97T, S252L, P256S, K406E, M585V, Y589D, K660M	[68, 117]
Colorectal cancer	R203H, R210Q, D334N, Q361R, L552I, P583L, R665W, E778K.	[118-120]
Endometrial cancer	D101Y, G227E, S252W, P253R, F276V, K310R, S373C, Y376C, C383R, A390T, M393R, V396D, L398M, I548D/V, N550H/K, K660E/M/N, C383R	[68, 109, 112, 121]
Gallbladder cancer	N550K, S252W	[118]
Gastric cancer	S267P, Q212K, G463E	[120, 122, 123]
Head and neck squamous cell cancer	N550D	[124]
Lung cancer	E116K, P253L, I381V, C383R, K421I, D480N, H545Q, G584V, I591M, Q621K, R626T, D138N, N211I, D247Y, D283N, W290C, G302W, S320C, E471Q, M538I, G584W, D603E, K660N/E, L773F, T787K	[102, 125-131]
Melanoma	S24F, V77M, H213Y, E219K, G227E, V248D, R251Q, G271E, G305R, T371R, E476K, D531N, E575K, E637K, M641I, I643V, A649T, S689F, G702S, P709S, R760Q, L771V	[132]
Oral cancer	V393A, G272V, P253R	[115, 130]
Spermatocytic seminoma	S252F/W, P253R/S, S267P, F276V, C278F, Y281C, Q289P, G336R, Y338C/H, C340F/R/S, S352C, K527E, N550K, K642R, K660E	[133]

Most of these point mutations of FGFR2 result in a gain of function of the protein. The mutations in the extracellular domain enhance the ligand-binding capability and change the ligand specificity [74, 75]. Some mutations in FGFR2 are also known to cause FGFR2 ligand independent dimerization of FGFR2,

leading to the activation of its kinase domain [2, 19]. We have had previously introduced the point mutation Ser252Trp (S252W) in mouse FGFR2 and established a mouse model for Apert syndrome (AS) [76]. The mutant mice exhibited severe craniosynostosis characterized by premature fusion of coronal suture, and shortened cranial base. *In vitro* analysis revealed that the FGFR2-S252W mutation increases apoptosis of osteogenic cells in mutant coronal suture, reduces the space between osteogenic fronts of flat bones, and causes the physical contact of these bones, leading to premature fusion of the coronal suture [76]. Further analysis demonstrated that the S252W mutation activates FGFR2-MAPK-ERK signaling which in turn, triggers bax mediated apoptosis [77].

On the other hand, reports also revealed that R251Q mutation in FGFR2 diminishes its ligand binding affinity [10]. V248D, G227E and G271E mutations impair FGFR2 dimerization, while A648T, D530N and I642V mutations reduce kinase activity [10]. Thus different point mutations of FGFR2 could have different impacts on the functions of FGFR2 and its downstream signaling due to the different nature of the mutations; thus the actual impact of these mutations need to be carefully studied individually.

Strategies for inhibition of FGFR2 signaling as the therapeutic target

Based on the nature of mutations in FGFR2, many approaches can be employed to target FGFR2 signaling for diseases, i.e. targeting FGFR2, the receptors themselves, and downstream signaling molecules. However, as the family of FGFRs share high structural similarity [17], many compounds not only inhibit FGFR2, but other FGFRs as well. Consequently, it is difficult to develop chemical compounds that are highly specific for FGFR2 only. Recently, four inhibitors (ADZ4547, BGJ398, Dovitinib and Lucitanib) have entered phase II trials, and two of them, ADZ4547 and BGJ398, have shown strong specificity to FGFR2 [78-80].

It was shown that FGFR2 signaling mediates resistance to small molecule inhibitors through switching of the HER2 signaling pathway [81]. Studying a cell line, UACC812, which was derived from a lapatinib-resistant breast cancer, Azuma *et al.* (2011) found these cells contain marked amplification of the FGFR2 gene, which serves as a vital factor for the survival of the resistance breast cancer cell as they become independent of the HER2 pathway [81]. This study suggests that the development of inhibitors to target FGFR2 might become a new therapy strategy to treat HER2-amplified breast cancer patients.

To decrease the side effects of targeting FGFR2, therapeutic antibodies may have much benefit, as they introduced to reduce the potential toxicity of pan-FGFR inhibition for the treatment cancer cells. So far, antibodies targeting FGFR3 have been shown to inhibit bladder cancer and the proliferation of myeloma cells [82, 83], suggesting developing clonal antibodies is a promising field. Otherwise, PDZ173074 and pazopanib showed sensitivity of the FGFR fusion-positive cell line SW780 [84]. It has been shown that breast cancer patients with FGFR2 fusion may benefit from targeted FGFR2 kinase inhibition [85, 86]. Recently, Sommer *et al.* (2016) developed a novel FGFR2 antibody–drug conjugates (FGFR2-ADC) [87]. In this case, auristatin (a microtubule-disrupting cytotoxic drug) is conjugated to a FGFR2 monoclonal antibody that binds to both FGFR2-IIIb and FGFR2-IIIc isoforms through a non-cleavable linker. Their data demonstrated that the FGFR2-ADC can inhibit growth of FGFR2-positive cell line (MFM-223) and its derived xenograft tumor models with more than 100-fold higher efficiency than FGFR2-negative cell lines [87].

Conclusion and future perspectives

Advances in our understanding of FGFR2 signaling over the past decade have been dramatic. Basic studies into the structure, genetics, cellular biology, and biochemistry of FGFR2 have yielded mounting information regarding how FGFR2 acts through its downstream signaling pathways. The molecular mechanisms underlying activation of FGFR2 is now well understood, but it is also a major challenge to gain more knowledge for future development. Importantly, SNPs in FGFR2 play a vital role in increasing the risk for breast cancer through their interactions with transcription factors to promote tumor formation. Of note, among the 29 SNPs in FGFR2 reviewed here, some of them were associated with luminal A, luminal B (ER/PR+, HER2+), or HER2+/ER- disease, but none were associated with basal-like disease [48, 88]. The underlying mechanisms regarding their association with these particular subtypes of breast cancer is another key challenge for future studies. Furthermore, many point mutations have been found to be associated with various cancers. Although some signaling pathways, such as FGFR2-MAPK-ERK signaling, have been discovered, the mechanisms for each specific mutation for promoting specific types of cancer formation remain elusive. Finally, because large amount of cancers, including breast cancers bear amplification, SNP or point mutations in FGFR2, future efforts should be directed towards the discover of specific inhibitors for FGFR2, and clinical trials of these inhibitors in order to develop effective therapies

for FGFR2 associated diseases, including breast cancer.

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Competing Interests

The authors have declared that no competing interest exists.

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